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Investigating the Ibuprofen Chiral Forms Interactions with Single Wall Carbon Nanotube

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Abstract:
The aim of this study is investigating the transport mechanism of ibuprofen chiral isomers inside single wall carbon nano tube (SWCNT) using mathematical modeling. To achieve this goal, molecular dynamics simulation has been performed to evaluate the interactions of ibuprofen isomers with SWCNT in an aqueous solution. Results show that both chiral forms of ibuprofen molecules enter and remain inside SWCNT from their methyl side chains and their movement is not along the centerline of the tube. The distance of the closest atom of the drug molecule from SWCNT surface is around 2.26A˚. A tilted angle between ibuprofen molecule and internal surface of SWCNT is detected to be around 34◦. Moreover, these ibuprofen chiral forms interact to each other from their carboxylic side chain. This causes ibuprofen fluctuation inside SWCNT around the tube axis. Also, calculated results do not show any significant differences between selectivity of SWCNT toward R- and S- chiral forms of ibuprofen molecule. This confirms that both ibuprofen chiral forms have the same transport mechanism inside SWCNT.
Keywords: *Carbon nano tube, Molecular dynamics simulation, Chirality, Ibuprofen, Chiral forms.*

1. INTRODUCTION

Domestic wastewaters contain the variety of organic contaminants such as pharmaceuticals and personal care products [1-3]. Pharmaceuticals and antibiotics are the most abundant residual drugs in surface waters [4].
Most of these compounds are chiral. These chiral compounds often exhibit remarkably different effects in transport mechanism and separation technology. Also, they undergo both incomplete removal in wastewater treatment plants and slow natural degradation. Several methods have been reported for degrading emerging organic contaminants such as nanofiltration, adsorption, reverse osmosis, ozonation and chemical oxidation [5-9].
Among different proposed methods, adsorption process is one of the best. In adsorption, adsorbent properties have the main effects on the separation efficiency.
Recently, nano materials with large surface to volume ratio and specific physical and chemical properties attract more and more attention for biological separation. One of the best nano materials to achieve this goal is carbon nanotube (CNT) [10-12].
CNTs attractiveness comes from its unique physical, chemical, mechanical and thermal properties originating from the small size, cylindrical structure, and high aspect ratio of length to diameter. According to the experimental studies, it has been found that CNTs have good properties as adsorbent and transporter of bio-molecules including drugs [13], vaccines [14], small peptides [15], proteins [16] and nucleic acids [17].

Also they have relatively high adsorption affinity for aromatic compounds than no aromatics molecules [18]. Some experimental studies about the dynamic behavior of benzene, alkylated benzenes and alkylated naphthalenes indicate that the development of CNTs as potential materials for selective adsorption and shape-selective separation of aromatic molecules is necessary [19]. As biological molecules mostly composed of aromatic groups, these observations confirm the ability of CNTs for adsorption of biological molecules.

In the present study, the ability of CNTs for removing the ibuprofen chiral isomers from water has been studied. Ibuprofen is one of the most pharmaceutical compounds in waste water. As, most of the biological compounds are chiral, both chiral forms of ibuprofen molecules have been selected in this study.

Molecular dynamics simulation (MD) has been applied to investigate the solute interactions with CNT surface. Exploring the molecular interactions between CNTs and biological materials will provide key information on the application of nanotubes in both scientific and industrial fields.

2. MATERIALS AND METHODS

To investigate the interactions of ibuprofen molecules with carbon nanotube, a racemic mixture of ibuprofen molecule as a high polar and chiral molecule in an aqueous solution is constructed.

2.1. Ibuprofen

Ibuprofen is an important pharmaceutical compound with the systematic name 2-(4-isobutylphenyl) propanoic acid and $(CH_3)_2CHCH_2C_6H_4CH(CH_3)$ COOH chemical structure [20]. It has two different chiral forms: R- and S- isomers. S-ibuprofen exhibits pharmacological effects but R-form is inactive. A unidirectional inversion from the R- to S-form occurs during metabolism [21]. So, both chiral forms of this molecule can be finding in waste water.

Indeed, removing both chiral forms of ibuprofen enantiomers from water is necessary. Figures (1-a) and (1-b) show the chiral structures of this molecule. The approximate width and length of this molecule is 4 and 10 Å, respectively. Figure (1-c) shows the radial distribution function (RDF) of both chiral ibuprofen molecules.

From RDF curve, it can be found that there is not any difference between R- and S- isomers from chemical structure which has been expected. Also, they have the same atomic Millikan charge. The only difference between R & S isomers is their spatial structure. This property produces different interactions between these isomers with the environment. Also, there is not any inter-conversion between these two chiral forms during the MD simulation.

2.2. Single Wall Carbon Nano Tube

A rigid armchair (10,10) single wall carbon nano tube with 1.35 nm diameter and 5 nm length is selected for simulation (Figure 1-d). The diameter and the length of SWCNT has been selected according ibuprofen size. When the diameter of SWCNT is larger than ibuprofen length, the probable movement of the drug molecule from its largest length can be occurred. By selecting the length of SWCNT much more than two drug lengths, the movement of two drug molecules simultaneously inside SWCNT can be followed.

2.3. Molecular dynamics simulation

Molecular dynamics simulation is performed using Gromacs software [22]. Canonical ensemble (NVT) has been selected for simulation at constant temperature of 300 K. NVT is an appropriate and common ensemble in order to compute transport mechanism in simulations. Also, the produced conditions in this ensemble is very close to the experimental conditions in laboratories for transport experiments.

To maintain a constant temperature, Berendsen thermostat has been applied. The periodic boundary conditions are used. The simulated system includes of two R- and S- ibuprofen molecules, one SWCNT and 3000 water molecules to produce a fully hydrated box with the approximate density of 998 kg. m^{-3} (near the water bulk density at the temperature of 300 K).

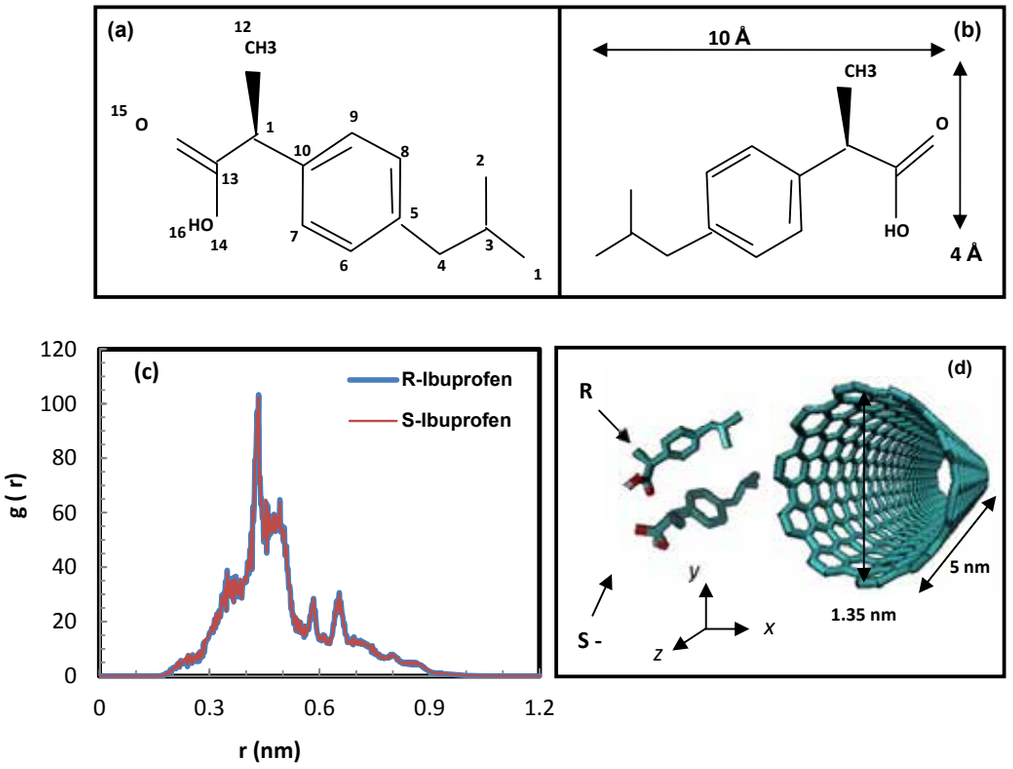

Figure 1: *Schematic of chiral forms of ibuprofen molecule (a) S-ibuprofen and (b) R-ibuprofen, (C) RDF of both chiral forms of ibuprofen and (d) the initial structure of the simulated system without water.*

The size of the system is 3.3 nm * 3.3 nm * 9.4 nm. The tube has been placed at the center of the box to produce a unique structure in all directions and ibuprofen molecules are placed manually near the entrance of the tube.

Figure 2 shows the initial box. Gromos 96 is used as an appropriate force filed [23]. In this force field, the interactions between the atoms are divided into a non-bonded part between any pair of atoms that are within a given cutoff radius and the bonded parts between the atoms connected chemically.

In the case of non-bond Coulombic and van der Waals interactions, partial charges and parameters for the repulsive and attractive parts of the interactions are assigned to each atom. The bonded interactions consist of the stretching (two body interactions), covalent bond angle (three-body interactions), and the dihedral (four-body interactions) terms. The total potential energy U is written as:

$$U = U_{stretching} + U_{angle} + U_{dihedral} + U_{nonbond} \quad (1)$$

Here, $U_{stretching}$ is the bond-stretching potential, given by:

$$U_{stretching} = \sum_{bonds} \frac{1}{2} k_{ij} (r_{ij} - r_0)^2 \quad (2)$$

where r_{ij} is the distance between the centers of atoms i and j, with r_0 being the equilibrium length of the bond, and k_{ij} a force constant.

The potential U_{angle} represents the energy associated with the change in the bonds' angle, and is given by:

$$U_{angle} = \sum_{\theta ijk} \frac{1}{2} k_{\theta ijk} (\theta_{ijk} - \theta^0_{ijk})^2 \quad (3)$$

with Θ^0_{ijk} being the equilibrium angle and $k_{\theta ijk}$ a force constant.

The torsional rotational potential is a periodic

function with an m-fold barrier,

$$U_{dihedral} = \frac{1}{2}k_{\emptyset}[1 + \cos(m\emptyset - \emptyset_0)] \quad (4)$$

where m is the dihedral multiplicity, Φ_0 the equilibrium value of the angle, and k_Φ a force constant.

The non-bond part of the potential energy is given by:

$$U_{nonbond} = \sum_{i<j}\left\{4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \frac{erfc(-\beta r_{ij})}{4\pi\varepsilon_0 r_{ij}} q_i q_j\right\} \quad (5)$$

Here, q_i is the partial charge of atom i, β is a parameter that determines the space sum's relative weight, erfc is the complementary error function, and σ_{ij} and ε_{ij} are the Lennard-Jones size and energy parameters, respectively. The Lorentz-Bertelot rules have been used for calculation of sigma and epsilon for different atom types according equations 6 and 7 [21].

$$\sigma_{ij} = \frac{1}{2}(\sigma_{ii} + \sigma_{jj}) \quad (6)$$

$$\varepsilon_{ij} = (\varepsilon_{ii}\varepsilon_{jj})^{\frac{1}{2}} \quad (7)$$

For water molecules, SPC model [24] has been applied. All the applied bonded and non-bonded interactions parameters for ibuprofen and CNT have been taken from Gromos 96 force field library [23] and are shown in Table 1. It should be emphasized that the selected SWCNT in this study is idealized and therefore not completely realistic, i.e. no hydrogen atoms nor functional groups are considered at the open cap of the nanotube.

Also, SWCNT has been selected as a rigid nano tube and unaffected by the adsorption. This means that no force field parameters for C(SWCNT)-C(SWCNT) interaction and therefore internal motion of the nanotube is not included in this study. An alternative for future developments could be to use more sophisticated models. Nevertheless, the futures described in this paper and the conclusions are not essentially affected by a more involved force field for C(SWCNT)-C(SWCNT) atoms.

The electrostatic interactions in the simulations are calculated using the particle-mesh Ewald (PME) method [25]. A cut off radius of 1.2 nm has been selected for both electrostatic and van der Waals interactions.

By using cut off radius, the interactions between the atoms are divided into a nonbond part -between any pair of atoms that are within the given radius - and the bonded parts between the atoms connected chemically. Selected cut off value is larger than the length and diameter of ibuprofen molecules. As SWCNT is selected as a rigid nano tube and unaffected by the adsorption, 1.2 nm is a safe value for van der Waals interactions of ibuprofen molecules with CNT surface, too.

At first, system is energy minimized for 200 ps and after that MD simulation is performed for 8 ns using a time step of 2 fs. Equilibration state is monitored by calculating the total energy of the system versus the simulation time which is typically achieved after 1 ns. Visualization is done using VMD package.

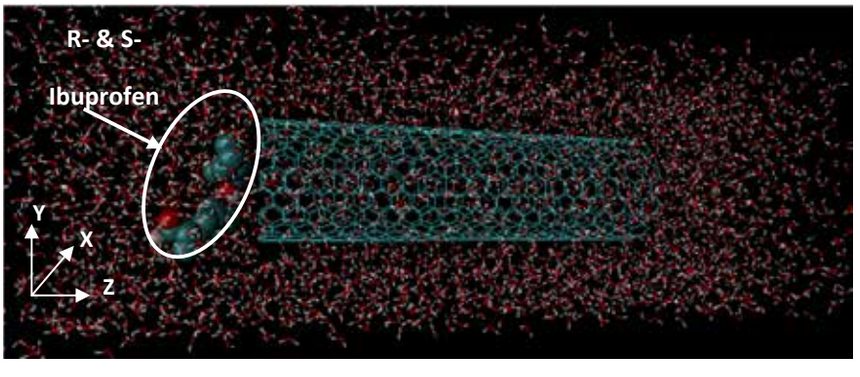

Figure 2: *Initial structure of the simulated system with water molecules. Ibuprofen molecules are shown with VDW model.*

Table 1: *Bonded and non-bonded parameters of ibuprofen and SWCNT atoms based on Gromos 96 force field.*

Bonded Parameters		
Bond	**K (KJ.mol^{-1})**	**r_0 (nm)**
CH_3-CH	334720	0.153
CH-CH_3(chiral)	334720	0.153
CH-CH_2	334720	0.153
CH_2-C(aromatic)	334720	0.153
CH-C(aromatic)	418400	0.139
CH-CH (aromatic)	418400	0.139
C (aromatic)-CH	334720	0.153
CH-C (carboxylic)	334720	0.153
C (carboxylic)-O(hydroxyl)	418400	0.125
C (carboxylic)-O(carbonyl)	418400	0.125
C-C (SWCNT)	418400	0.14
Angle	**K (KJ.mol^{-1})**	**Θ_0 (º)**
CH_3-CH-CH_3	460	111
CH_3-CH-CH_2	460	111
CH-CH_2-C(aromatic)	460	111
CH_2-C(aromatic)-CH	418.4	120
C(aromatic)-CH-CH	418.4	120
CH-C(aromatic)-CH	418.4	120
C(aromatic)-CH-CH_3(chiral)	460	109.5
C(aromatic)-CH-C(carboxyl)	460	109.5
CH-C(carboxylic)-O(hydroxyl)	502	117
O(hydroxyl)-C(carboxyl)-O(carbonyl)	502	117
C-C-C (SWCNT)	418.4	120
Dihedral	**K (KJ.mol^{-1})**	**Ψ_0 (º)**
C(aromatic)-CH-CH-CH_2	1673	0
C(aromatic)-CH-CH-CH	1673	0
C(carboxyl)-CH-O(carbonyl)-O(hydroxyl)	1673	0
CH-CH_3-CH_3-CH_2	836	35.3
CH- C(aromatic)-CH_3-C(carboxyl)	836	35.3
C-C-C-C (SWCNT)	15.15	180
Non bonded Parameters		
Atom	**ε / k_B (K)**	**σ (nm)**
C	28.1	0.34
O	80.5	0.303

3. RESULTS AND DISCUSSION

3.1. Ibuprofen displacement

At the first stage, the displacement of ibuprofen molecules along x, y and z axes is calculated as a function of the simulation time. Figures 3 and 4 show the displacement of ibuprofen molecules versus the simulation time and Figure 5 shows the schematic of the system after the simulation. As Figures 3 shows both chiral forms of ibuprofen molecules enter from their methyl side chains (smallest side of the molecule) and remain inside SWCNT at the middle part of CNT.

Figure 4 shows ibuprofen molecules like to locate near the internal surface of CNT (Figure 4-a and 4-b) and they are never seen at the inner and outer surfaces of CNT from the two ends of SWCNT after the equilibrium time (Figure 4-c).

Ibuprofen molecules do not place inside nano tube parallel to CNT axis along the z axis and there is an angle between drugs and CNTs surface (Figure 5-a). Also, ibuprofen molecules interact to each other from their carboxylic side chains (Figure 5-b). These observations are well supported by density profile (Figure 6).

Figure 6-a shows that in the direction perpendicular to the tube surface (x-axis), ibuprofen molecules prefer to move near the internal surface of CNT along the z-axis and their favorite motion is 2.26 ˚A away from the inner surface of CNT (Figure 6-a). In the direction along the z-axis, only one peak is observed that indicates the ibuprofen tendency for remaining at the middle part of the tube (Figure 6-b).

3.2. Ibuprofen alignment inside SWCNT

To understand more details about alignment of ibuprofen inside SWCNT, the atom-atom radial distribution functions (RDFs), expressed as gij (r) - the probability of finding a particle of type j in a sphere of radius, r, around a particle of type i - are calculated (Figure 7).

Interest here is focused onto the ibuprofen initial, chiral and last side chains (methyl, methyl and carboxylic groups). Therefore, in this study, i denotes the atoms of ibuprofen (C_1, C_2, C_4, C5, C_{12}, O_{14} and O_{15}) and *j* represents the carbon atoms of the SWCNT. Calculated RDFs are summarized in Figure 7-a, whilst a schematic representation of the drug–SWCNT complex is shown in Figure 7-b. The RDF plots are detected for C_1, C_2, C_4, C_5, C_{12}, O_{14} and O_{15} at 4.34 Å, 4.92 Å, 4.14 Å, 4.92 Å, 4.58 Å, 5.60 Å and 5.60 Å. The minimum distance of ibuprofen atoms from internal surface of SWCNT is belonging to C_4 atom.

Using the probable distances from the C_4 (4.14 ˚A) and C_5 (4.92 ˚A) atoms to the SWCNT surface, and the C_4–C_5 distance (1.39 A˚), the angle between the drug and tube axis can be estimated (Figure 5-a and 7-b). The obtained value is 34◦ indicates the tilted angle between C_4 atom of ibuprofen and the inner surface of the SWCNT.

This interaction is supposed to be the main reason why the preferential mobility of the drug molecule along the molecular z-axis of the SWCNT takes place at 2.26˚A far from the surface of the SWCNT (Figure 5-b and 6-a). From calculations it can be find that the biggest distances between ibuprofen chiral molecules take place from their methyl side chains and the smallest distances is related to the carboxylic side chains. This confirms that ibuprofen molecules interact to each other from their carboxylic side chains (Figure 8). Similar this behavior has been observed in another MD simulation [26] for similar drug molecule.

3.3. Ibuprofen dipole moment

Ibuprofen molecules alignment inside SWCNT creates a fluctuating dipole moment along x and y-axes (Figure 9-a and 9-b). However, a positive sign in dipole moment along z-axis is approximately observed for both chiral molecules (Figure 9-c). This indicates that both ibuprofen molecules inter and remain inside SWCNT with the same direction along the z-axis and inversely change their positions along the tube diameter. This is in agreement with previous observations which discussed in above sections (see Figures 3,5 and 8).

3.4. Heat of adsorption

At last to understand the adsorption mechanism of drug molecules in SWCNT, some further

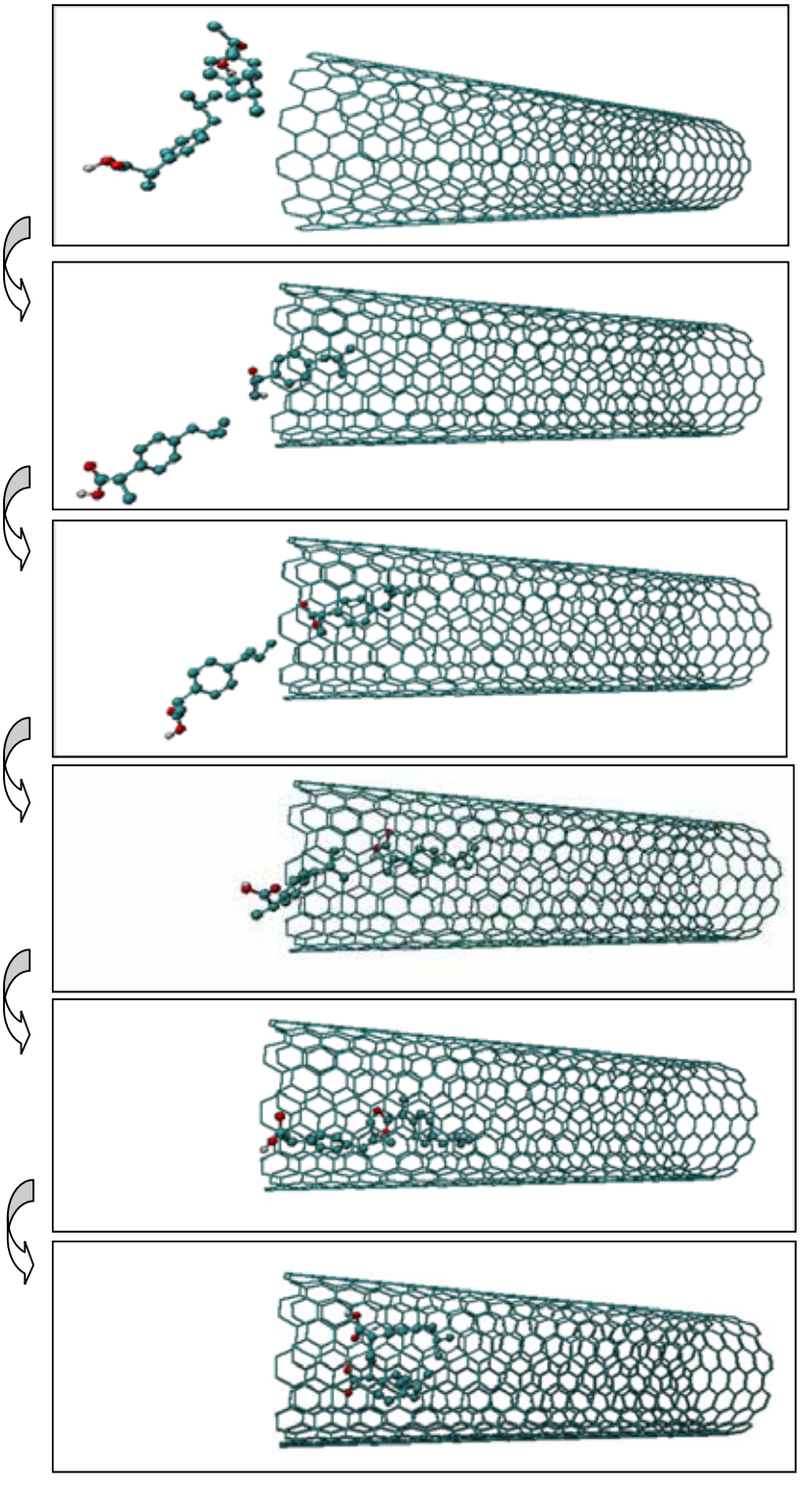

Figure 3: *Ibuprofen molecules transport inside SWCNT at different simulation time.*

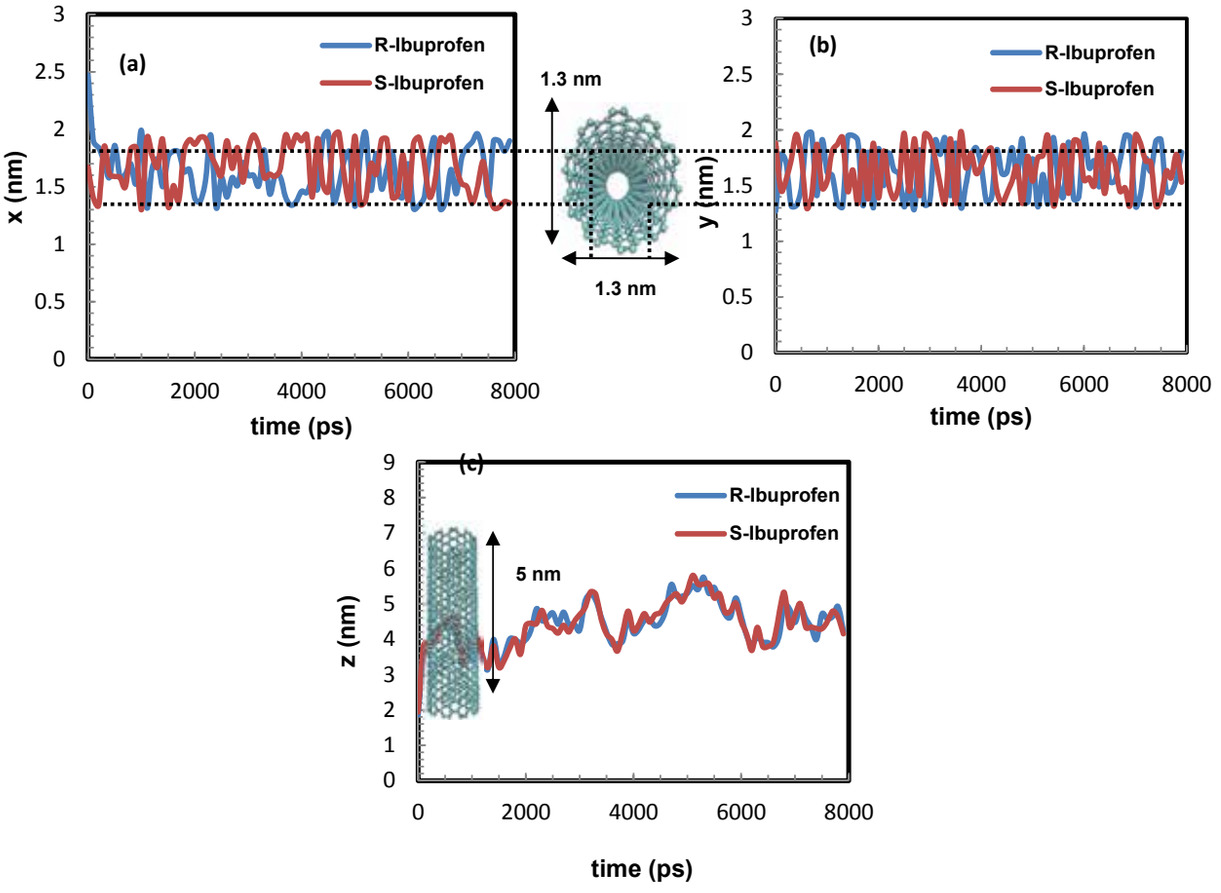

Figure 4: *Ibuprofen coordination inside SWCNT along (a) x, (b) y and (c) z axes.*

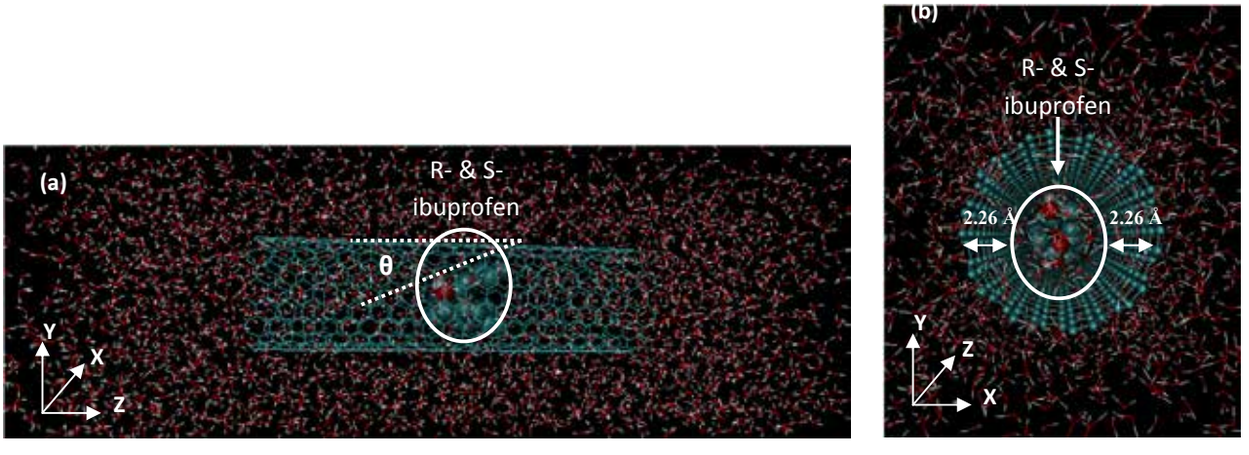

Figure 5: *Ibuprofen molecules inside SWCNT after simulation, (a) side view, (b) front view.*

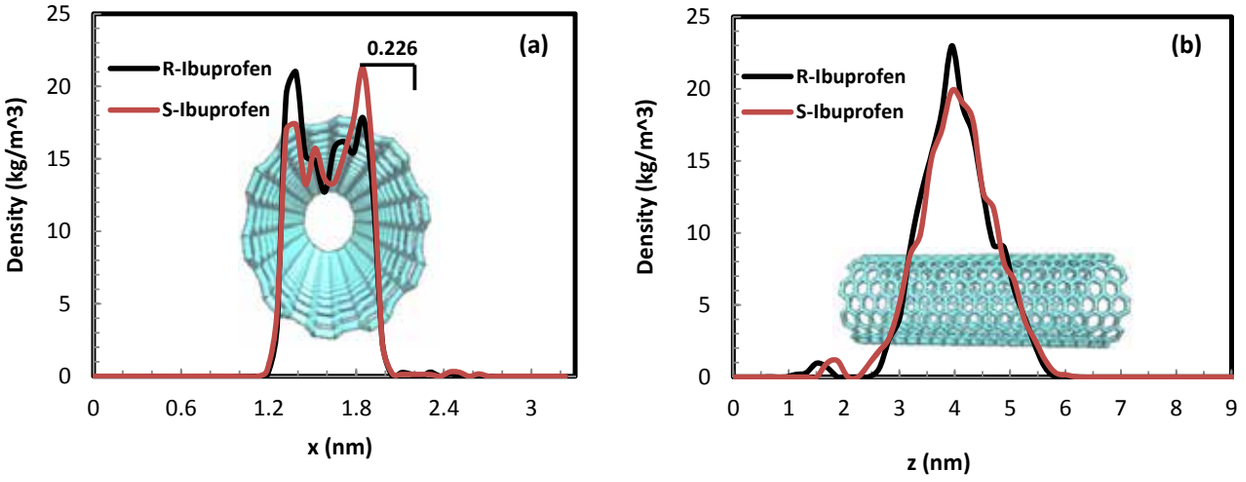

Figure 6: *Density distribution of ibuprofen molecules inside SWCNT along (a) x axis and (b) z axis.*

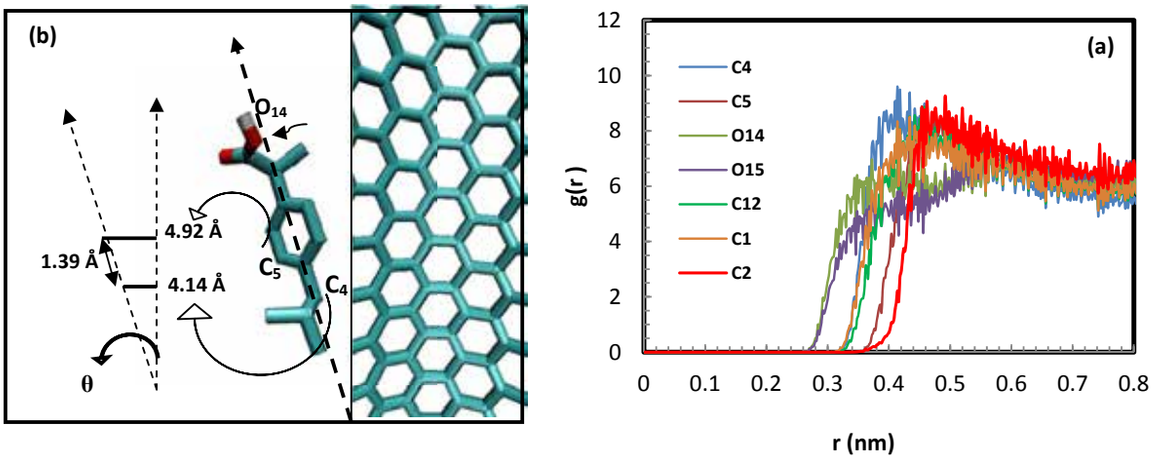

Figure 7: *(a) RDF of various atoms of ibuprofen molecule inside SWCNT, (b) schematic of angle between C_4 and SWCNT surface.*

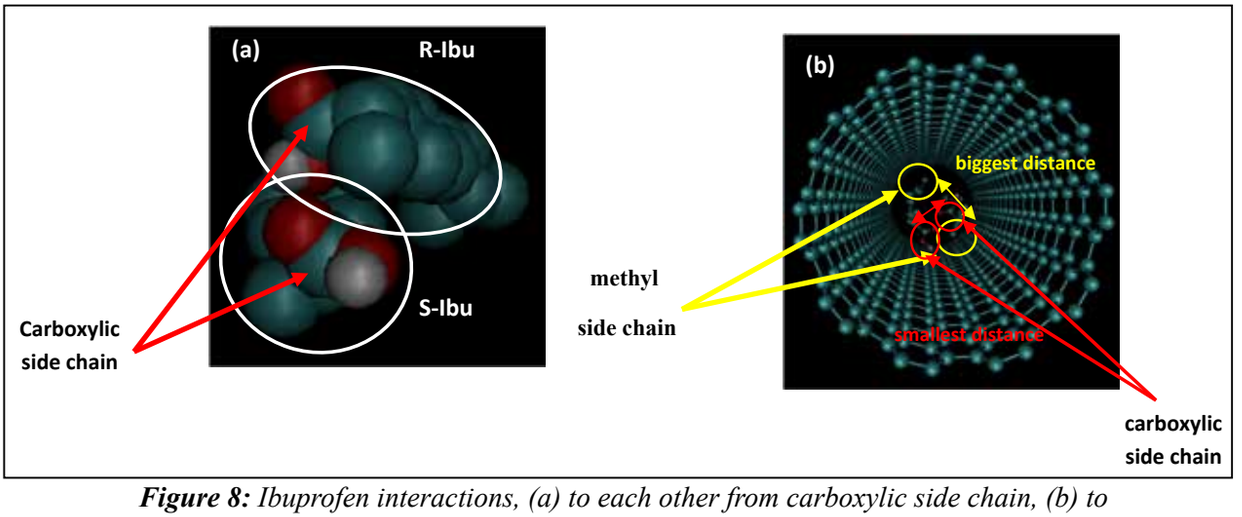

Figure 8: *Ibuprofen interactions, (a) to each other from carboxylic side chain, (b) to SWCNT surface from methyl side chain.*

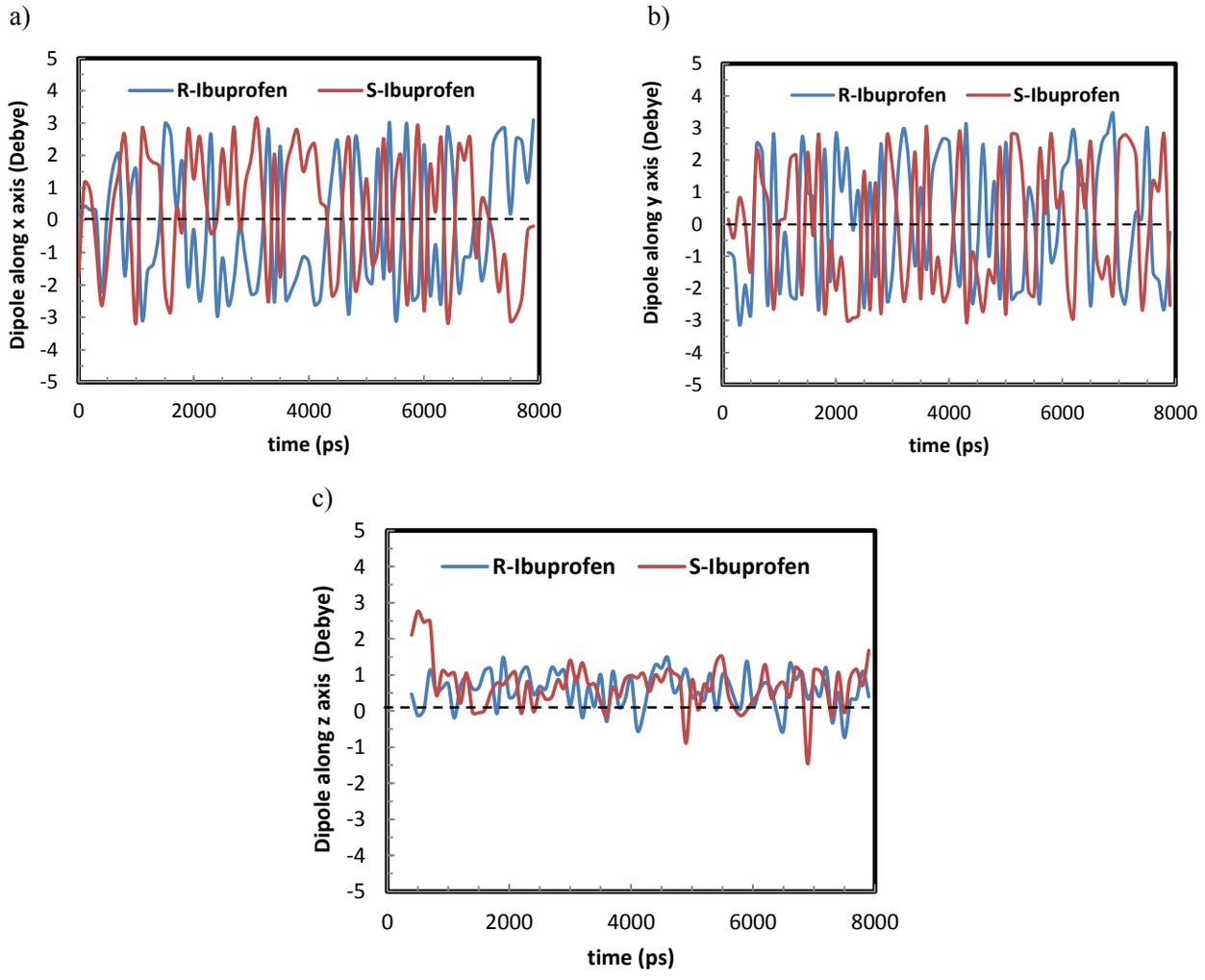

Figure 9: *Distribution of ibuprofen dipole moments along (a) x, (b) y and (c) z axes.*

simulations have been performed to compute the heat of adsorption. For computation of the heat of adsorption (adsorption energy) [27] , the total energy of the MD simulation is obtained by time averaging the sum of energies in the entire simulation course and then utilized to define the heat of adsorption using equations 8 and 9.

Calculated results show that ibuprofen salvation in water (Eq.9) is an endothermic process with the salvation energy of 335.741 kJ/mol. Also, ibuprofen adsorption from an aqueous solution in SWCNT is an exothermic process with 945.4 kJ/mol heat of adsorption.

4. CONCLUSIONS

MD simulations provide insight into the structural properties of SWCNT to remove ibuprofen drug molecules from water. According to the local density distributions of the drug projected to the diameter and the length of the SWCNT, both chiral forms of ibuprofen molecules are able to transfer from bulk inside SWCNT and there is not any differences between ibuprofen chiral forms selectivity inside SWCNT.

In the other word, there is not any significant difference for adsorption of chiral forms of ibuprofen

inside SWCNT. This confirms the ability of SWCNT to remove both chiral forms of big similar biological molecules from aqueous solution. Also, ibuprofen molecule's movement is not along the centerline of the tube and the drug molecules' displacement is at a distance of 2.26 ˚A from the inner surface of the tube, where the C_4 atom of ibuprofen is oriented with a 34◦ tilted angle to the SWCNT inner surface. These observations are approved by calculation of dipole moment of drug molecules along x, y and z axes. Finally, ibuprofen adsorption on the CNT is an exothermic process.

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